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(54) **Pyrimidopyrimidine derivatives.**

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EP-A- 0 175 652
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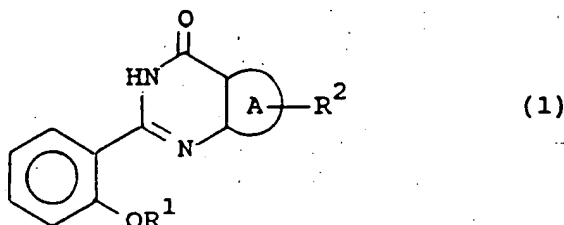
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Description

The present invention relates to pyrimidopyrimidine derivatives, processes for their preparation, intermediates in their preparation, their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combatting such conditions where such inhibition is thought to be beneficial. They are bronchodilators and are therefore of use in combatting chronic reversible obstructive lung diseases such as asthma and bronchitis. Some of the compounds of the present invention have anti-allergic activity and are therefore useful in combatting allergic diseases such as allergic asthma, allergic rhinitis, urticaria and irritable bowel syndrome. Furthermore the compounds of this invention are vasodilators and are therefore of value in combatting angina, hypertension and congestive heart failure. DE-A-1620561, DE-A-1795722 and GB-A-1543874 disclose pyrimidopyrimidine and quiazoline derivatives.

Accordingly the present invention provides compounds of the formula (1):



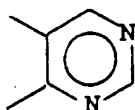
and pharmaceutically acceptable salts thereof, wherein

R¹ is C₁-₆ alkyl, C₂-₆ alkenyl, C₃-₅ cycloalkyl, C₁-₆ alkyl, or C₁-₆ alkyl substituted by 1 to 6 fluoro groups;

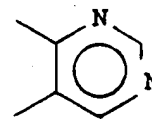
R² is C₁-₆ alkylthio, C₁-₆ alkylsulphonyl, C₁-₆ alkoxy, hydroxy, hydrogen, hydrazino, C₁-₆ alkyl, phenyl, -NHCOR³ wherein R³ is hydrogen or C₁-₆ alkyl, or -NR⁴R⁵, wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R⁴ and R⁵ are independently hydrogen, C₃-₅ cycloalkyl or C₁-₆ alkyl which is optionally substituted by -CF₃, phenyl, -S(O)ₙC₁-₆ alkyl wherein n is 0, 1 or 2, -OR⁶, -CO₂R⁷ or -NR⁸R⁹ wherein R⁶ to R⁹ are independently hydrogen or C₁-₆ alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -S(O)ₙC₁-₆ alkyl, -OR⁶ or -NR⁸R⁹ groups; and



is a ring of sub-formula (a) or (b):



(a)



(b).

Suitably R¹ is C₂-₅ alkyl for example ethyl, n-propyl, isopropyl, butyl, isobutyl or pentyl.

Suitably R¹ is C₃-₅ alkenyl for example propenyl, butenyl or pentenyl.

Suitably R¹ is cyclopropylmethyl.

Examples of C₁-₆ alkyl substituted by 1 to 6 fluoro groups include -CF₃, -CH₂CF₃ or -CF₂CHFCF₃.

Preferably R¹ is n-propyl.

Suitably R^2 is C_{1-6} alkylthio, C_{1-6} alkylsulphonyl or C_{1-6} alkoxy for example methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, methoxy, ethoxy or propoxy.

Suitably R^2 is hydroxy, hydrogen or hydrazino.

Suitably R^2 is phenyl or C_{1-6} alkyl for example methyl, ethyl or propyl.

5 Suitably R^2 is $-NHCOR^3$ for example formamido or acetamido.

Suitably R^2 is $-NR^4R^5$ for example amino, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, cyclopropylamino, morpholino, 2,2,2-trifluoroethylamino, phenethylamino, 3-methylthiopropylamino, 3-methylsulphinylpropylamino, 3-methylsulphonylpropylamino, 2-hydroxyethylamino, 3-hydroxypropylamino, 2-hydroxypropylamino, 3-methoxypropylamino, N-ethyl-N-(2-hydroxyethyl)amino, 2-aminoethylamino, 2-dimethylaminoethylamino, ethoxycarbonylmethylamino, carboxymethylamino, 2-ethoxycarbonylmethylamino or 2-carboxyethylamino.

Suitably

15



is a group of sub-formula (a) thus forming a pyrimido[4,5-d]pyrimidine ring system.

20 Suitably



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is a group of sub-formula (b) thus forming a pyrimido[5,4-d]pyrimidine ring system.

Particular compounds of this invention are :

- 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 30 7-methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 35 7-amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 40 7-ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-(2-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 45 7-morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-(3-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 50 7-(2-methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-(2-dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-(2-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-(3-methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-(2-aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine hydrochloride,
- 55 7-(3-methylsulphinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 7-(3-methylsulphonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
- 4,7-dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidine,
- 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,

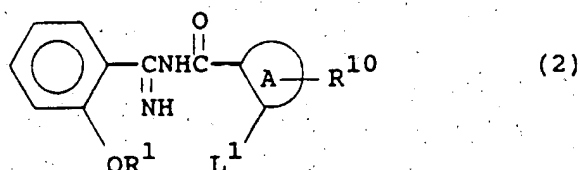
- 7-diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-ethoxycarbonylethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 15 7-(carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2,2,2-trifluoroethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 10 7-(N-ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine, or
 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[5,4-d]pyrimidine,
 or pharmaceutically acceptable salts thereof.
- 15 This invention covers all tautomeric and optical isomeric forms of compounds of formula (1).
 Compounds of the formula (1) wherein R^2 is $-NR^4R^5$ or hydrazino may form pharmaceutically acceptable salts with acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acids.
 Compounds of the formula (1) may form pharmaceutically acceptable salts with metal ions, such as alkali metals for example sodium and potassium, or with an ammonium ion.
- 20 In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.
- Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, transdermally, rectally,
 25 via inhalation or via buccal administration.
- Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition
 30 is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include starch, celluloses, lactose, sucrose and magnesium stearate. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions
 35 may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.
- Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.
- 40 A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats.
- Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.
- 45 Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.
- Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.
- 50 Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base.
- The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a
 55 compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered as required for example

from 1 to 8 times a day or by infusion. The compositions of the invention are bronchodilators and are useful in chronic reversible obstructive lung disease for example asthma and bronchitis. In addition some of the compositions of the present invention have anti-allergic activity and are useful in combatting allergic diseases such as allergic asthma, allergic rhinitis, urticaria and irritable bowel syndrome. The compositions of the present invention also have vasodilator activity and are of use in the treatment of angina, hypertension and congestive heart failure. Such conditions can be treated by administration orally, topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, sulbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H₁-antagonists, vasodilators for example hydralazine, angiotensin converting enzyme inhibitors for example captopril, anti-anginal agents for example isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate, anti-arrhythmic agents for example quinidine, procainamide and lignocaine, calcium antagonists for example verapamil and nifedipine, diuretics such as thiazides and related compounds for example bendrofluzide, chlorothiazide, chlorothalidone, hydrochlorothiazide, and other diuretics for example frusemide and triamterene, and sedatives for example nitrazepam, flurazepam and diazepam.

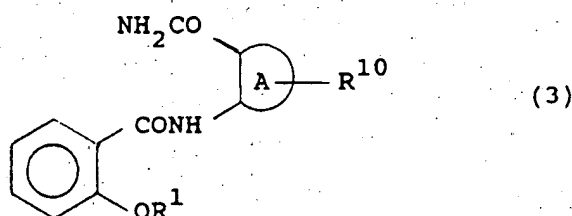
In another aspect the present invention provides a process for the preparation of compounds of the formula (1) or pharmaceutically acceptable salts thereof, which process comprises :

a) cyclising a compound of the formula (2) :



wherein L¹ is a displaceable group, R¹ and A are as hereinbefore defined, and R¹⁰ is a group R² as hereinbefore defined or a precursor thereof; or

b) cyclising a compound of the formula (3) :



wherein R¹, R¹⁰ and



are as hereinbefore defined; and thereafter where necessary :

- converting a group R¹⁰ to a group R²;
- optionally forming a pharmaceutically acceptable salt.

Suitably the cyclisation of a compound of the formula (2) is performed in the presence of a base such as an alkali metal carbonate or triethylamine, in an aprotic solvent such as dimethylformamide, acetonitrile or N-methylpyrrolidone, at ambient or an elevated temperature, for example 50-170 °C, conveniently at the reflux temperature of the reaction mixture. Suitably L¹ is halo for example bromo or chloro.

5 Suitably a compound of the formula (3) is cyclised by heating at an elevated temperature, for example 50-150 °C, in the presence of an acid or a base in a suitable solvent such as aqueous C₁₋₄ alcohols, water, toluene, a halohydrocarbon or acetonitrile. Conveniently a compound of the formula (3) is cyclised by heating in pyridine or aqueous base such as sodium hydroxide at the reflux temperature of the reaction mixture.

10 Examples of R¹⁰ being a precursor to a group R² is when R¹⁰ is a halo or C₁₋₆ alkylthio group. Such groups can be converted to a -NR⁴R⁵ group by reaction with an amine HNR⁴R⁵ in a suitable solvent such as a C₁₋₄ alkanol or pyridine at an elevated temperature, for example 50-120 °C, conveniently in a pressure vessel.

A compound of the formula (1) wherein R² is C₁₋₆ alkylthio can suitably be converted to the
15 corresponding compound wherein R² is C₁₋₆ alkylsulphonyl by reaction with an oxidising agent, for example with at least two equivalents of a peroxy acid such as m-chloroperoxybenzoic acid.

A compound of the formula (1) wherein R² is C₁₋₆ alkylsulphonyl can suitably be converted to the corresponding compound wherein R² is -NR⁴R⁵ by reaction with an amine HNR⁴R⁵ in a suitable solvent such as a halohydrocarbon or toluene at ambient or elevated temperature for example 40-100 °C.

20 A compound of the formula (1) wherein R² is C₁₋₆ alkylsulphonyl can suitably be converted to the corresponding compound wherein R² is C₁₋₆ alkoxy by reaction with a C₁₋₆ alkoxide, eg an alkali metal C₁₋₆ alkoxide such as sodium methoxide or ethoxide, in a C₁₋₆ alkanol at ambient or elevated temperature, for example 40-100 °C.

A compound of the formula (1) wherein R² is C₁₋₆ alkylthio can suitably be converted to the
25 corresponding compound wherein R² is hydrazino by reaction with hydrazine.

A compound of the formula (1) wherein R² is hydrazino can be converted to the corresponding compound wherein R² is hydrogen by treatment with silver oxide.

A compound of the formula (1) wherein R² is hydroxy can suitably be prepared by reacting a compound of the formula (1) wherein R² is C₁₋₆ alkylthio with an alkali metal C₁₋₆ alkoxide such as sodium methoxide
30 or ethoxide under aqueous work-up conditions.

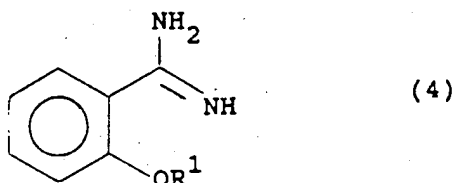
A compound of the formula (1) wherein R² is C₁₋₆ alkoxy can be converted to the corresponding compound wherein R² is hydroxy by hydrolysis, for example by treatment with hydrochloric acid.

A compound of the formula (1) wherein R² is amino can suitably be converted to the corresponding compound where R² is -NHCOR³ by reaction with a formylating or C₂₋₇ alkanoylating agent. Examples of
35 such reagents include formic acid, C₁₋₆ alkyl formate, formamide, acetic anhydride, propionic anhydride or acetylchloride.

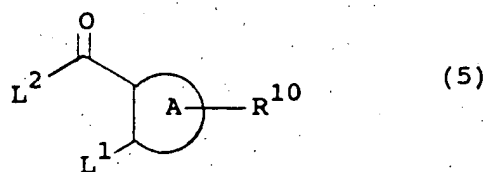
A compound of the formula (1) wherein R⁴ or R⁵ is C₁₋₆ alkyl substituted by C₁₋₆ alkylthio can suitably be converted to the corresponding compound wherein R⁴ or R⁵ is C₁₋₆ alkyl substituted by C₁₋₆ alkylsulphanyl by reaction with one equivalent of an oxidising agent such as a peroxy acid, for example
40 m-chloroperoxybenzoic acid. The C₁₋₆ alkylsulphanyl compound can similarly be oxidised to a compound of the formula (1) wherein R⁴ or R⁵ is C₁₋₆ alkyl substituted by C₁₋₆ alkylsulphonyl.

A compound of the formula (1) wherein R⁴ or R⁵ is C₁₋₆ alkyl substituted by -CO₂R⁷ in which R⁷ is C₁₋₆ alkyl can suitably be hydrolysed by reaction with aqueous base, for example aqueous sodium hydroxide to form the corresponding compound wherein R⁷ is hydrogen.

45 The compounds of the formula (2) can be prepared by reaction of a compound of the formula (4) :



55 wherein R¹ is as hereinbefore defined,
with a compound of the formula (5) :

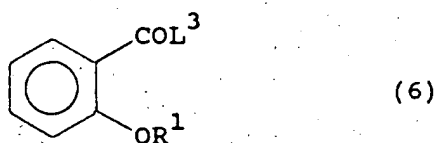


10 wherein L^2 is a leaving group and L^1 , R^{10} and are as hereinbefore defined.

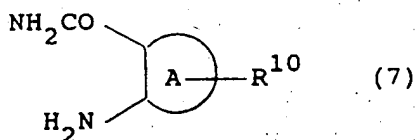


Suitably L^2 is C_{1-6} alkoxy or halo for example methoxy, ethoxy, chloro or bromo. Conveniently a solution of a compound of the formula (4) is initially formed by treatment of an acid addition salt of a compound of the formula (4) with a suitable base, for example triethylamine, a sodium alkoxide or sodium hydride, in an organic solvent such as a C_{1-4} alcohol, acetonitrile or dimethylformamide and the solution is then treated with a compound of the formula (5) at a moderate temperature for example 0-60 °C, conveniently ambient, to afford a compound of formula (2). Suitable acid addition salts are those formed with inorganic acids such as hydrochloric or sulphuric acid or with strong organic acids such as methanesulphonic or p-toluenesulphonic acid. Suitably a compound of the formula (2) is isolated and is then cyclised as hereinbefore described. Alternatively, a compound of the formula (2) is not isolated but is cyclised in situ by stirring at ambient or an elevated temperature, for example 40-170 °C.

A compound of the formula (3) can be prepared by reaction of a compound of the formula (6) :



35 wherein R^1 is as hereinbefore defined and L^3 is halo; with a compound of the formula (7) :



45 wherein R^{10} and



are as hereinbefore defined.

Suitably L^3 is chloro or bromo. Suitably a compound of the formula (6) is reacted with a compound of the formula (7) at ambient or elevated temperature e.g. 50-100 °C in a suitable solvent such as toluene, acetonitrile or a halohydrocarbon e.g. chloroform or dichloromethane, optionally in the presence of a base such as pyridine or triethylamine, to form a compound of the formula (3) which may be cyclised in situ or may be isolated and thereafter cyclised as hereinbefore described.

The compounds of the formula (4) and acid addition salts thereof are known or preparable in conventional manner from US Patent 3819631.

The compound of the formula (5) are known or can be prepared by methods known in the art.

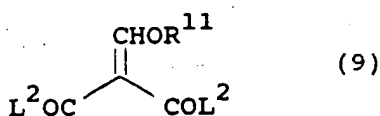
For example a compound of the formula (5) wherein



10 is a group of sub-formula (a), L¹ is halo, L² is C₁₋₆alkoxy and R¹⁰ is in the 2-position of the pyrimidine ring can be prepared by reaction of a compound of the formula (8) :



20 wherein R¹⁰ is as hereinbefore defined, with a compound of the formula (9) :



30 wherein R¹¹, is C₁₋₆alkyl and L² is as hereinbefore defined, and thereafter by reaction with a halogenating agent.

Suitable halogenating agents include thionyl chloride, phosphorous oxychloride or phosphorous tribromide.

A compound of the formula (5) wherein



40 is a group of sub-formula (a), L¹ and L² are chloro and R¹⁰ is 2-chloro can be prepared by reacting 2,4-dihydroxypyrimidine-5-carboxylic acid with phosphorous oxychloride.

A compound of the formula (5) wherein



is a group of sub-formula (a), L¹ is chloro, L² is ethoxy and R¹⁰ is 2-methylthio is commercially available (Aldrich Chemical Co Ltd).

A compound of the formula (5) wherein



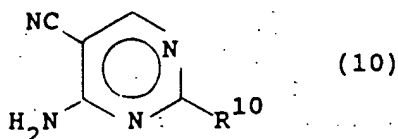
is a group of sub-formula (b), L¹ is bromo, L² is chloro and R¹⁰ is in the 2-position of the pyrimidine ring can be prepared by reaction of a compound of the formula (8) as hereinbefore defined with mucobromic acid and thereafter by reaction with a chlorinating agent such as thionyl chloride.

The compound of the formula (7) are known or can be prepared by methods known in the art.

For example a compound of the formula (7) wherein



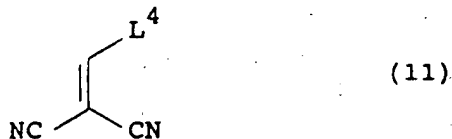
is a group of sub-formula (a) and R¹⁰ is in the 2-position of the pyrimidine ring can be prepared by hydrolysing a compound of the formula (10) :



wherein R¹⁰ is as hereinbefore defined.

Suitably a compound of the formula (10) is hydrolysed by treatment with concentrated sulphuric acid or by treatment with hydrogen peroxide and potassium hydroxide.

A compound of the formula (10) can be prepared by reacting a compound of the formula (8) as hereinbefore defined with a compound of the formula (11) :



wherein L⁴ is a leaving group.

Examples of L⁴ include C₁₋₆alkoxy, C₁₋₆alkylthio or halo such as chloro or bromo. Suitably L⁴ is C₁₋₆alkoxy.

Alternatively a compound of the formula (7) wherein



is a group of sub-formula (a) and R¹⁰ is hydrogen can be prepared by reacting a compound of the formula (8) wherein R¹⁰ is hydrogen with cyanoacetamide (Chem. Ber. 98, 3883 (1965)).

Pharmaceutically acceptable acid addition salts of the compounds of the formula (1) wherein R² is -NR⁴R⁵ or hydrazino may be prepared from the corresponding base of the compounds of the formula (1) in conventional manner. For example the base may be reacted with an acid in a C₁₋₄alkanol, or an ion-exchange resin may be used. The salts of the compounds of the formula (1) may be interconverted using ion-exchange resins. Non-pharmaceutically acceptable salts are therefore of use as they can be converted to pharmaceutically acceptable salts.

Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the compound of the formula (1) with a solution of the base.

The following biological test methods, data and Examples serve to illustrate this invention.

Bronchodilatation - In vivo

Male guinea-pigs of the Dunkin Hartley strain (500 - 600g) were anaesthetised with Sagatal (pentobarbital sodium) (60 mg/kg). Airway resistance was measured using a modification of the classical Konzett-Rossler technique (J. Pharm. Methods, 13, 309-315, 1985). U46619 (9,11-methanoepoxy-PGH₂) was infused i.v. at a rate of 2.5 nmol/min, this produced a steady state of bronchoconstriction (approximately 120% increase from basal airway resistance). The compound under test was administered by i.v. bolus injection, and the subsequent peak inhibition of bronchoconstriction recorded.

The dose of compound required to reduce the U46619-induced bronchoconstriction by 50% is given as the BD₅₀. The compounds of Examples 1, 7, 8, 12, 13, 14, 18, 20, 21, 22 and 24 had BD₅₀ values in the range 0.48 - 3.85 μ mol/kg. These results demonstrate in vivo anti-bronchoconstrictor activity.

Vasodilatation - In vivo

Male Wistar rats (300 g) were anaesthetised with a sodium 5-ethyl-5-(1-methylpropyl)-2-thiobarbiturate/sodium pentobarbitone mixture i.p. (62.5 and 22.5 mg/kg respectively). The trachea was cannulated and the rats breathed spontaneously air enriched with O₂ (5 ml/min). Blood pressure was recorded from a carotid artery and a jugular vein was cannulated for the administration of compounds. The temperature of the animal was maintained at 37°C by the use of an electric blanket. The abdominal aorta was separated from the inferior vena cava, distal to the renal arteries and was cannulated centrally to supply the perfusion pump with blood and distally for the perfusion of the hind quarters at constant pressure. The perfusion circuit was primed with 5% bovine serum albumin dissolved in 0.9% sodium chloride solution, pH adjusted to 7.4. Initially the pump rate was set between 10 and 15 ml/min to match the hind quarter perfusion pressure to that of the systemic circulation. Once set, the pressure remained unaltered for the rest of the experiment. A change in the speed of the pump (equivalent to hindquarter blood flow) was used to assess the changes in hindquarter vascular resistance. All compounds were administered as a bolus i.v. The compound of Example 1 caused a 43.7% increase in hindquarter blood flow at a dose of 50 μ mol/kg.

Anti-allergic activity

Male Duncan Hartley guinea-pigs (250-300 g) were sensitised to ovalbumen by i.p. injection of 2 ml of 50mg.ml⁻¹ i.p. and 0.2 ml s.c. Three weeks later they were anaesthetised with 60mg.kg⁻¹ sodium pentobarbitone. The trachea was cannulated and the animal respired at a rate of 40 breaths per minute and at an initial tracheal inflation pressure of 16 mmHg. Tracheal inflation pressure was measured by a transducer connected to a side arm of the respiration circuit. The carotid artery was cannulated for the measurement of blood pressure and the signal was used to trigger an instantaneous rate meter. A jugular vein was cannulated for the administration of drug and allergen. After surgery the animals were allowed to stabilise and the drug was administered i.v. as a bolus. Following this, ovalbumen 1mg.kg⁻¹ was injected i.v. as the antigen challenge either 2, 15 or 30 minutes following drug treatment and the peak bronchoconstrictor response recorded. For the control group ovalbumen only was given. One ovalbumen challenge per guinea-pig was used and n = 6 for each time point. The percentage increase in tracheal inflation pressure was calculated. The following results indicating an anti-allergic activity were obtained.

Compound of Example	Dose μ mol/kg	% Inhibition of Control Bronchoconstrictor Response 30 min after drug administration
8	6.0	23
12	18.7	24
13	4.8	21
18	22.6	44
24	6.5	24

Phosphodiesterase activity

The activity of the compounds of the present invention as inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase was measured using the procedure described in European Patent Application No. 293063. The compounds of Examples 1 to 29 and 31 to 38 had IC₅₀ values (the concentration of inhibitor

required for 50% inhibition of enzyme activity) in the range 0.2 to 27 μ M. The compounds of the present invention have the advantage that they are selective in not inhibiting cyclic AMP phosphodiesterase (type III).

5 Example 1

7-Methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine

2-Propoxybenzamidinium (from sodium, 0.3 g, in ethanol, 50 ml, and 2-propoxybenzamidinium hydrochloride, 2.77 g) was dissolved in 2-propanol (20 ml) and the resulting cooled (2 °C) solution was added to a cooled (2 °C) solution of ethyl 4-chloro-2-methylthio-5-pyrimidine carboxylate (2 g) in 2-propanol (30 ml). The reaction mixture was stirred at 2 °C for 2 hours and was then left overnight at ambient temperature to yield a white crude product, 1.18 g, m.p. 179-181 °C. Recrystallisation from ethanol yielded the title compound, 0.92 g, m.p. 186-187 °C.

15 Example 2

7-Methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine

2-Ethoxybenzamidinium (from sodium, 0.08 g, in ethanol, 10 ml, and 2-ethoxybenzamidinium hydrochloride, 0.70 g) was dissolved in acetonitrile (10 ml) and the resulting cooled (2 °C) solution was added to a cooled (2 °C) suspension of ethyl 4-chloro-2-methylthio-5-pyrimidine carboxylate (0.81 g) in acetonitrile (10 ml). The reaction mixture was stirred at 2 °C for one hour. Triethylamine (0.35 g) was added and the reaction mixture was stirred at ambient temperature for 21 hours to yield a white precipitate, 0.22 g, which was collected by filtration. The filtrate was reduced in volume under reduced pressure to yield a second crop of solid, 0.41 g. The products were combined and recrystallised from ethanol to yield the title compound, 0.30 g, m.p. 224.5-225.5 °C.

30 Example 3

7-Methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine

2-Methoxybenzamidinium (from sodium, 0.15 g, in ethanol, 20 ml, and 2-methoxybenzamidinium methanesulphonate, 1.70 g) was dissolved in acetonitrile (20 ml) and the resulting cooled (2 °C) solution was added to a cooled (2 °C) suspension of ethyl 4-chloro-2-methylthio-5-pyrimidine carboxylate (2.33 g) in acetonitrile (20 ml). Triethylamine (0.66 g) was added and the reaction mixture was stirred at 2 °C for one hour and at ambient temperature for 18 hours. Acetonitrile was removed under reduced pressure and water (25 ml) was added. The mixture was cooled and a white solid was collected, washed with water and recrystallised from ethanol to yield the title compound, 0.46 g, m.p. 229-231 °C (dec.).

40 Example 4

7-Methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine

Ethyl 4-chloro-2-methylthio-5-pyrimidine carboxylate (1.50 g) followed by triethylamine (0.65 g) was added to a stirred mixture of 2-isobutoxybenzamidinium hydrochloride (1.46 g) and triethylamine (0.65 g) in acetonitrile (150 ml). The reaction mixture was stirred at 5 °C for 15 minutes and then at ambient temperature for 3 days. A solid (0.55 g) was collected by filtration and the filtrate was reduced in volume to yield a second crop of solid (0.47 g). The solids were combined and recrystallised from ethanol to yield the title compound, 0.57 g, m.p. 185-186 °C.

50 Example 5

7-Methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine

In a similar manner to Example 4 reaction of ethyl 4-chloro-2-methylthio-5-pyrimidine carboxylate (1.50 g) with 2-cyclopropylmethoxybenzamidinium hydrochloride (1.45 g) and triethylamine (1.30 g) in acetonitrile (50 ml) yielded a white solid (1.18 g) which was collected, dissolved in chloroform and the chloroform

solution was extracted twice with 2 Normal hydrochloric acid. The chloroform solution was evaporated under reduced pressure and the residue was recrystallised from ethanol to yield the title compound, 0.52 g, m.p. 186-187 °C.

5 Example 6

7-Methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine

2-Allyloxybenzamidinium (from sodium, 0.22 g, in ethanol, 100 ml, and 2-allyloxybenzamidinium hydrochloride, 2.00 g) was dissolved in acetonitrile (50 ml) and the resulting cooled (2 °C) solution was added to a cooled (2 °C) solution of ethyl 4-chloro-2-methylthio-5-pyrimidine carboxylate (2.19 g) in acetonitrile (50 ml). The temperature was allowed to rise and the reaction mixture was stirred overnight at ambient temperature. The volume of the reaction mixture was reduced by evaporation under reduced pressure to yield a solid (0.96 g) which was collected. More product (0.45 g) precipitated from the filtrate. The combined products were recrystallised twice from ethanol to yield the title compound, 340 mg, m.p. 205-206 °C.

Example 7

7-Amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine

7-Methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (1.55 g) was heated in ethanolic ammonia (50 ml) in a pressure vessel for 8 hours at 90 °C and then for 8 hours at 145 °C. After cooling a grey solid (0.64 g) was collected and was recrystallised from ethanol (with charcoal) to yield a crude product (0.47 g) which was recrystallised from ethanol to yield the title compound, 0.29 g, m.p. 261-262 °C.

Example 8

7-Methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine

7-Methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (1.40 g) was treated with a solution of methylamine in industrial methylated spirit (33%; 30 ml) in a pressure vessel for 9 hours at 90 °C. The reaction mixture was evaporated under reduced pressure to yield a cream solid which was dissolved in chloroform. The organic solution was washed with water, dried (magnesium sulphate) and evaporated under reduced pressure to yield a cream solid. Elution from silica with chloroform:methanol (25:1) yielded a crude product which was recrystallised twice from ethanol to yield the title compound, 0.31 g, m.p. 235-236 °C.

Example 9

7-Dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine

7-Methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.60 g) was treated with a solution of dimethylamine in industrial methylated spirit (33%; 20 ml) in a pressure vessel for 18 hours at 90 °C. The cooled reaction mixture was evaporated under reduced pressure to yield a solid which was dissolved in aqueous sodium hydroxide. The filtered aqueous solution was neutralised with a few drops of concentrated hydrochloric acid to yield a pale yellow solid which was recrystallised from 2-propanol to yield the title compound, 0.33 g, m.p. 177.5-178.5 °C.

50 Example 10

7-Hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine

A stirred mixture of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (1.31 g) and hydrazine hydrate (3 ml) in ethanol (30 ml) was heated under reflux for 3 hours to yield a yellow precipitate. The reaction mixture was cooled overnight and the yellow precipitate was collected and washed with ethanol and water to yield the title compound, 0.80 g, m.p. 219-220 °C.

Example 11**4-Oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido [4,5-d]pyrimidine**

5 A mixture of 7-hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.40 g) and silver oxide (0.32 g) in methanol (40 ml) was stirred at ambient temperature for 18 hours and at 45-50 °C for 24 hours. The cooled reaction mixture was evaporated under reduced pressure and the residue was eluted from a silica column with chloroform. The combined fractions containing product were evaporated under reduced pressure to yield a white solid which together with another sample (27 mg), similarly prepared, was
 10 recrystallised from 2-propanol to yield the title compound, 136 mg, m.p. 142-143 °C.

Example 12**7-Ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

15 In a similar manner to Example 9 reaction of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.60 g) and 33% ethylamine in ethanol (20 ml) yielded the title compound, 0.29 g, m.p. 181-182 °C (recrystallised from ethanol/water and then from ethanol).

Example 13**7-(2-Hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

25 A stirred mixture of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.60 g) and ethanolamine (0.25 ml) in ethanol (20 ml) was heated under reflux for 19 hours. More ethanolamine (0.75 ml) was added and stirring under reflux continued for 16 hours. A white crystalline solid which precipitated from the cooled reaction mixture was collected, washed with cold ethanol and recrystallised from ethanol to yield the title compound, 0.38 g, m.p. 204-205.5 °C.

Example 14**7-Ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

35 In a similar manner to Example 3 reaction of ethyl 4-chloro-2-ethyl-5-pyrimidine carboxylate (0.86 g) with 2-propoxybenzamidine (from sodium, 0.1 g, in ethanol, 10 ml, and 2-propoxybenzamidine methanesulphonate, 1.20 g) and triethylamine (0.4 g) in acetonitrile (25 ml) for 3 days at ambient temperature yielded a crude product, which was recrystallised twice from 2-propanol-ether to yield the title compound, 95 mg, m.p. 118-119 °C.

Example 15**7-Methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido [4,5-d]pyrimidine**

45 In a similar manner to Example 8 reaction of 7-methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine (0.75 g) and 33% methylamine in industrial methylated spirit (25 ml) for 18 hours yielded the title compound, 0.38 g; m.p. 265-267 °C (recrystallised twice from methanol).

Example 16**7-Phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

55 In a similar manner to Example 3 reaction of ethyl 4-chloro-2-phenyl-5-pyrimidine carboxylate (1.05 g) with 2-propoxybenzamidine (from sodium, 0.10 g, in ethanol, 10 ml, and 2-propoxybenzamidine methanesulphonate, 1.20 g) and triethylamine (0.40 g) in acetonitrile (25 ml) for 3 days at ambient temperature yielded a crude product which was recrystallised from methanol to yield the title compound, 0.52 g, m.p. 203-4 °C.

Example 17**7-Morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

- 5 A stirred solution of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.60 g) and morpholine (1.25 g) in pyridine (20 ml) was heated under reflux for 45 hours. The reaction mixture was evaporated under reduced pressure to yield a crude product which was washed with water and twice recrystallised from methanol to yield the title compound, 0.25 g, m.p. 175.5-177 °C.

10 Example 18**7-Cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro pyrimido[4,5-d]pyrimidine**

- 15 A stirred mixture of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.60 g) and cyclopropylamine (1.2 ml) in ethanol (20 ml) was heated for 18 hours at 90 °C in a pressure vessel. Further cyclopropylamine (1 ml) was added and the reaction mixture was stirred in a pressure vessel for 18 hours at 100 °C and then for 20 hours at 120 °C. The cooled reaction mixture was evaporated under reduced pressure to yield a residue which was dissolved in 1 Normal sodium hydroxide. The resultant solution was treated with charcoal, filtered and the filtrate neutralised by the addition of concentrated
20 hydrochloric acid which caused the precipitation of a crude product. The crude product was eluted from a silica column with chloroform as eluant, and the combined fractions containing product were evaporated under reduced pressure to yield a residue. This was twice recrystallised from methanol to yield the title compound, 0.23 g, m.p. 207.5-208.5 °C.

25 Example 19**7-Acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

- 30 A stirred mixture of 7-amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.59 g) and acetic anhydride (5 ml) was heated under reflux for 1.5 hours. Excess acetic anhydride was removed under reduced pressure. The solid residue was washed with water and triturated with hot methanol to yield the title compound, 0.57 g, m.p. 273-4 °C.

Example 20

35

7-Propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine

- In a similar manner to Example 9 reaction of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.60 g) and n-propylamine (1.44 g) in ethanol (20 ml) yielded the title
40 compound, 0.46 g, m.p. 185-7 °C (recrystallised from ethanol).

Example 21**7-(3-Hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

45

- In a similar manner to Example 13, reaction of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.45 g) and 3-amino-1-propanol (0.98 g) in ethanol (15 ml) yielded the title compound, 0.31 g, m.p. 185-6 °C (recrystallised from ethanol).

50 Example 22**7-(2-Methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

- In a similar manner to Example 13, reaction of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.41 g) and methoxyethylamine (1.04 g) in ethanol (15 ml) for 48 hours
55 yielded the title compound, 0.38 g, m.p. 193-4 °C (recrystallised twice from methanol).

Example 23**7-(2-Dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

5 In a similar manner to Example 13, reaction of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.49 g) and N,N-dimethylethylenediamine (1.24 g) in ethanol (20 ml) yielded the title compound, 0.46 g, m.p. 181-2 °C (recrystallised for methanol).

Example 24**7-(2-Hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

10 In a similar manner to Example 13 reaction of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.41 g) and 1-amino-2-propanol (0.97 g) in ethanol (15 ml) for 40 hours yielded the title compound 0.37 g, m.p. 212.5-214 °C (recrystallised from methanol).

Example 25**7-(3-Methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

20 In a similar manner to Example 13 reaction of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.79 g) and methylthiopropylamine (0.50 g) in ethanol (15 ml) for 40 hours yielded a crude product which was purified by elution from silica with 40-60 ° petroleum ether : chloroform (gradient elution) to yield the title compound, 0.52 g, m.p. 173-4 °C (recrystallised from methanol).

Example 26**7-(2-Aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine hydrochloride**

30 A stirred solution of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.49 g) and ethylenediamine (0.90 g) in ethanol (15 ml) was heated under reflux for 21 hours. Ethanol was removed under reduced pressure and the residue was dissolved in 1 Normal hydrochloric acid. The acidic solution was extracted with chloroform (3 x 10 ml), neutralised (to pH 6-7) with 2 Normal sodium hydroxide and evaporated under reduced pressure to yield a crude product which was recrystallised from methanol to yield the title compound, 0.28 g, m.p. 210-2 °C.

Example 27**7-(3-Methylsulphinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

40 A cool (0 °C) solution of 7-(3-methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (1.84 g) and m-chloroperoxybenzoic acid (0.97 g) in dichloromethane (180 ml) was allowed to warm to ambient temperature with stirring. The solution was then stirred for 18 hours at ambient temperature and allowed to stand for 10 days. The reaction mixture was evaporated under reduced pressure and the residue eluted from a silica column with chloroform : methanol (gradient elution). The combined fractions containing product were evaporated under reduced pressure and the residue was recrystallised from isopropanol to yield the title compound, 1.73 g, m.p. 188-9 °C.

Example 28**7-(3-Methylsulphonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

55 A solution of 7-(3-methylsulphinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.80 g) and m-chloroperoxybenzoic acid (0.40 g) in dichloromethane (50 ml) was stirred at ambient temperature for 24 hours. During this time further m-chloroperoxybenzoic acid (about 200 mg) was added on 2 occasions. The solution was washed with dilute aqueous sodium bicarbonate (3 x 25 ml) and

the combined washings back-extracted with a little dichloromethane. The combined organic layer was washed with water and then brine, dried (magnesium sulphate) and evaporated under reduced pressure to yield a residue. This was recrystallised three times from methanol to yield the title compound, 0.51 g, m.p. 222-3 °C.

5

Example 29

4,7-Dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidine

10 7-Methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.66 g) and methanol (0.26 g) were added to a stirring suspension of sodium hydride (0.38 g, 50% suspension in oil) in dry dimethylsulphoxide (15 ml). The mixture was stirred at ambient temperature for 1.5 hours and at 70-80 °C for 18 hours. The cooled reaction mixture was poured into water (500 ml), then glacial acetic acid (0.46 ml) was added and the mixture was extracted with chloroform (200 ml and then 2 x 100 ml). The combined
15 extracts were washed with water, dried (magnesium sulphate) and evaporated under reduced pressure to yield a solid which was washed successively with ether and 40-60 ° petroleum ether and recrystallised from dimethylformamide : water to yield a crude product (0.18 g). This together with another sample (0.24 g) similarly prepared was eluted from a silica column with chloroform and 10% methanol in chloroform. The combined fractions containing product were evaporated under reduced pressure and the residue recrystallised from dimethylformamide : dilute hydrochloric acid and then from dimethylformamide to yield the title
20 compound, 0.15 g, m.p. 271-3 °C (decomposition).

Example 30

7-Methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine

A solution of 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (3.0 g) and m-chloroperoxybenzoic acid (3.8 g) in dichloromethane (180 ml) was stirred at ambient temperature for 3 hours and then allowed to stand for 3 days. The solution was washed with dilute aqueous sodium
30 bicarbonate (3 x 75 ml) and the combined washings extracted with dichloromethane (2 x 25 ml). The combined organic layers were washed successively with water and brine, dried (magnesium sulphate) and evaporated under reduced pressure to yield a crude product which was recrystallised from acetonitrile to yield the title compound, 2.04 g, m.p. 217-9 °C.

Example 31

7-Diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine

A solution of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (229
40 mg) and diethylamine (420 mg) in dichloromethane (8 ml) was stirred at ambient temperature for 3 hours. The reaction mixture was eluted from a silica column with diethyl ether : chloroform (4 : 1) and the combined fractions containing product were evaporated under reduced pressure to yield an oil which on trituration with 40-60 ° petroleum ether yielded the title compound, 85.5 mg, m.p. 116-7 °C.

Example 32

7-(2-Ethoxycarbonyl-ethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine

A solution of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (1.0 g),
50 β-alanine ethyl ester hydrochloride (1.10 g) and triethylamine (0.73 g) in dichloromethane (20 ml) was stirred at ambient temperature for 2.5 hours. The reaction mixture was extracted with dilute hydrochloric acid (20 ml) then water (10 ml), and the extracts back washed with dichloromethane (10 ml). The combined organic extracts were dried (magnesium sulphate) and evaporated under reduced pressure to yield a crude product which was recrystallised from ethanol : water to yield the title compound, 0.83 g, m.p. 142-3 °C.

55

Example 33**7-(Ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

5 In a similar manner to Example 32 reaction of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.86 g), glycine ethyl ester hydrochloride (0.65 g) and triethylamine (0.47 g) in dichloromethane (15 ml) yielded the title compound, 0.38 g, m.p. 174.5-176 °C (recrystallised from ethanol : water).

Example 34**7-(2-Carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

15 A solution of 7-(2-ethoxycarbonyl-ethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.53 g) in 1 Normal sodium hydroxide (5 ml) was stirred at ambient temperature for 2 hours. Acidification of the reaction mixture with concentrated hydrochloric acid yielded a precipitate which was recrystallised from ethanol : water to yield the title compound, 0.42 g, m.p. 227-8 °C.

Example 35**7-(Carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

20 In a similar manner to Example 34 reaction of 7-(ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.54 g) and 1 Normal sodium hydroxide (5 ml) yielded the title compound 0.41 g, m.p. 252-253.5 °C (dec.) (recrystallised from ethanol : water).

Example 36**7-Ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

30 A solution of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.50 g) in sodium ethoxide solution (from sodium, 0.16 g, and ethanol, 25 ml) was stirred at ambient temperature for 1.5 hours. Cooling and acidification of the reaction mixture with glacial acetic acid (0.42 g) yielded a precipitate which was twice recrystallised from ethanol to yield the title compound, 0.29 g, m.p. 196-197.5 °C.

Example 37**7-Methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

40 In a similar manner to Example 36 reaction of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.50 g) and sodium methoxide solution (from sodium, 0.16 g, and methanol, 20 ml) yielded the title compound, 0.29 g, m.p. 231-2 °C (recrystallised from methanol).

Example 38**7-(2,2,2-Trifluoroethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

50 A solution of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.72 g), 2,2,2-trifluoroethylamine hydrochloride (0.97 g) and triethylamine (0.73 g) in dichloromethane (15 ml) was stirred at ambient temperature for 48 hours and allowed to stand for 4 days. A yellow solid had formed which was collected by filtration and washed with dichloromethane. The filtrate was washed with dilute hydrochloric acid (15 ml) then water (10 ml) and the aqueous layers extracted with dichloromethane (2 x 7.5 ml). The combined organic layers were dried (magnesium sulphate) and evaporated under reduced pressure to yield a crude product. This was eluted from a silica column with diethyl ether : chloroform (4 : 1) and the combined fractions containing product were evaporated under reduced pressure to yield a residue which was recrystallised from isopropanol to yield the title compound, 0.13 g, m.p. 214-215.5 °C.

Example 39**7-Propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydr pyrimido[4,5-d]pyrimidine**

5 In a similar manner to Example 36 reaction of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.54 g) and sodium propoxide solution (from sodium, 0.17 g, and n-propanol, 25 ml) yielded the title compound, 0.19 g, m.p. 157-8 °C (recrystallised from n-propanol).

Example 40**7-(N-Ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

10 In a similar manner to Example 31 reaction of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.40 g) and 2-(ethylamino)ethanol (0.64 g) in dichloromethane (12 ml)
15 yielded the title compound, 137 mg, m.p. 141-2 °C (recrystallised from isopropanol-ether).

Example 41**7-Dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

20 In a similar manner to Example 31 reaction of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5d]pyrimidine (0.40 g) and dipropylamine (0.74 g) in dichloromethane (10 ml) yielded the title compound, 88 mg, m.p. 123-4 °C (recrystallised from cyclohexane).

Example 42**7-(2-Phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine**

25 In a similar manner to Example 31 reaction of 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (0.40 g) and phenethylamine yields the title compound.
30

Example 43

Pharmaceutical compositions for oral administration are prepared by combining the following :

	% w/w		
	0.5	3.0	7.14
7-Cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]-pyrimidine			
2% w/w Soya lecithin in soya bean oil	90.45	88.2	84.41
Hydrogenated vegetable shortening and beeswax	9.05	8.8	8.45

The formulations are then filled into individual soft gelatin capsules.

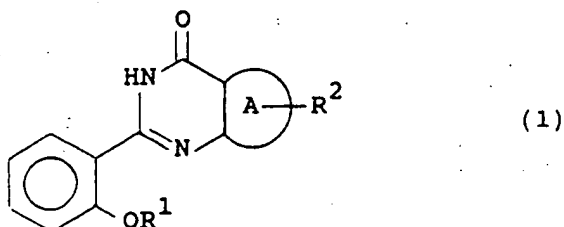
Example 44

45 A pharmaceutical composition for parenteral administration is prepared by dissolving the title compound of Example 13 (0.02 g) in polyethylene glycol 300 (25 ml) with heating. This solution is then diluted with
50 water for injections Ph. Eur. (to 100 ml). The solution is then sterilised by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

Claims

Claims for the following Contracting States: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula (1):



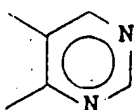
or a pharmaceutically acceptable salt thereof, wherein

R¹ is C₁-₆ alkyl, C₂-₆ alkenyl, C₃-₅ cycloalkyl, C₁-₆ alkyl substituted by 1 to 6 fluoro groups;

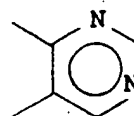
R² is C₁-₆ alkylthio, C₁-₆ alkylsulphonyl, C₁-₆ alkoxy, hydroxy, hydrogen, hydrazino, C₁-₆ alkyl, phenyl, -NHCOR³ wherein R³ is hydrogen or C₁-₆ alkyl, or -NR⁴R⁵, wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R⁴ and R⁵ are independently hydrogen, C₃-₅ cycloalkyl or C₁-₆ alkyl which is optionally substituted by -CF₃, phenyl, -S(O)-ₙC₁-₆ alkyl wherein n is 0, 1 or 2, -OR⁶, -CO₂R⁷ or -NR⁸R⁹ wherein R⁶ to R⁹ are independently hydrogen or C₁-₆ alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -S(O)-ₙC₁-₆ alkyl, -OR⁶ or -NR⁸R⁹ groups; and



is a ring of sub-formula (a) or (b):



(a)



(b)

2. A compound according to claim 1 wherein R¹ is C₂-₅ alkyl.
3. A compound according to claim 1 wherein R¹ is n-propyl.
4. A compound according to any one of claims 1 to 3 wherein R² is C₁-₆ alkylthio, C₁-₆ alkylsulphonyl or C₁-₆ alkoxy.
5. A compound according to any one of claims 1 to 3 wherein R² is hydrogen, hydroxy or hydrazino.
6. A compound according to any one of claims 1 to 3 wherein R² is phenyl or C₁-₆ alkyl.
7. A compound according to any one of claims 1 to 3 wherein R² is -NHCOR³ or -NR⁴R⁵.

8. A compound according to any one of claims 1 to 7 wherein



is a group of sub-formula (a).

9. A compound according to any one of claims 1 to 7 wherein



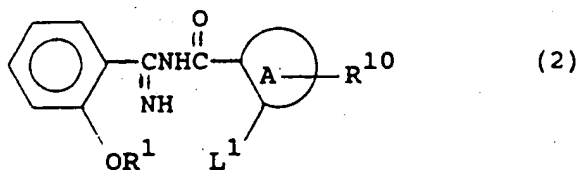
is a group of sub-formula (b).

10. A compound according to claim 1 which is :

- 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(3-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(3-methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine hydrochloride,
 7-(3-methylsulfinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(3-methylsulphonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 4,7-dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidine,
 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-ethoxycarbonylethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2,2,2-trifluoroethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,

7-(N-ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine, or
4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[5,4-d]pyrimidine,
or a pharmaceutically acceptable salt thereof.

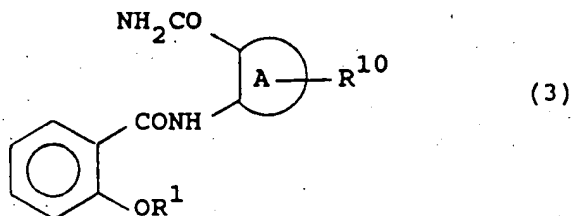
11. A compound according to any one of claims 1 to 10 for use as a medicament.
12. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier.
13. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises :
 - a) cyclising a compound of the formula (2) :



wherein L¹ is a displaceable group, R¹ and



are as defined in claim 1, and R¹⁰ is a group R² as defined in claim 1 or a precursor thereof; or
b) cyclising a compound of the formula (3) :



wherein R¹, R¹⁰ and



are as hereinbefore defined; and thereafter where necessary :

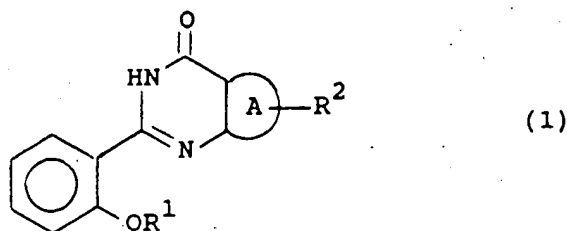
- converting a group R¹⁰ to a group R²;
- optionally forming a pharmaceutically acceptable salt.

14. A compound of the formula (2) as defined in claim 13.

15. A compound of the formula (3) as defined in claim 13.

Claims for the following Contracting State: ES

1. A process for preparing a compound of the formula (1) :



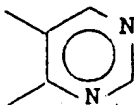
or a pharmaceutically acceptable salt thereof, wherein

R¹ is C₁-₆ alkyl, C₂-₆ alkenyl, C₃-₅ cycloalkyl, C₁-₆ alkyl, or C₁-₆ alkyl substituted by 1 to 6 fluoro groups;

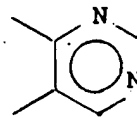
R² is C₁-₆ alkylthio, C₁-₆ alkylsulphonyl, C₁-₆ alkoxy, hydroxy, hydrogen, hydrazino, C₁-₆ alkyl, phenyl, -NHCOR³ wherein R³ is hydrogen or C₁-₆ alkyl, or -NR⁴R⁵, wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R⁴ and R⁵ are independently hydrogen, C₃-₅ cycloalkyl or C₁-₆ alkyl which is optionally substituted by -CF₃, phenyl, -S(O)-C₁-₆ alkyl wherein n is 0, 1 or 2, -OR⁶, -CO₂R⁷ or -NR⁸R⁹ wherein R⁶ to R⁹ are independently hydrogen or C₁-₆ alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -S(O)C₁-₆ alkyl, -OR⁶ or -NR⁸R⁹ groups; and



is a ring of sub-formula (a) or (b) :



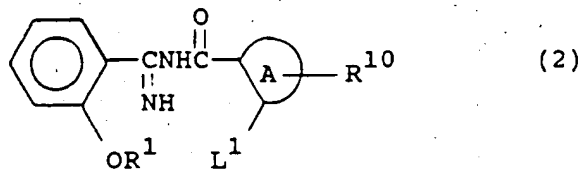
(a)



(b) ,

which process comprises:

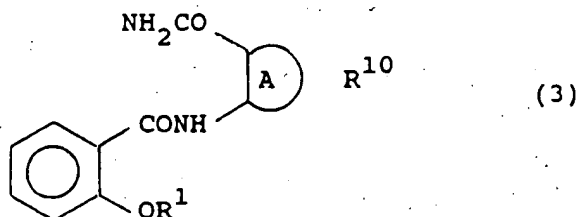
a) cyclising a compound of the formula (2) :



wherein L¹ is a displaceable group, R¹ and



are as hereinbefore defined and R^{10} is a group R^2 as hereinbefore defined or a precursor thereof; or
b) cyclising a compound of the formula (3) :



wherein R^1 , R^{10} and



are as hereinbefore defined;
and thereafter where necessary :

- converting a group R^{10} to a group R^2 ;
- optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 for preparing a compound wherein R^1 is C_{2-5} alkyl.
3. A process according to claim 1 for preparing a compound wherein R^1 is n-propyl.
4. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is C_{1-6} alkylthio, C_{1-6} alkylsulphonyl or C_{1-6} alkoxy.
5. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is hydrogen, hydroxy or hydrazino.
6. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is phenyl or C_{1-6} alkyl.
7. A process according to any one of claims 1 to 3 for preparing a compound wherein R^2 is $-NHCOR^3$ or $-NR^4R^5$.
8. A process according to any one of claims 1 to 7 for preparing a compound wherein



is a group of sub-formula (a).

9. A process according to any one of claims 1 to 7 for preparing a compound wherein

5



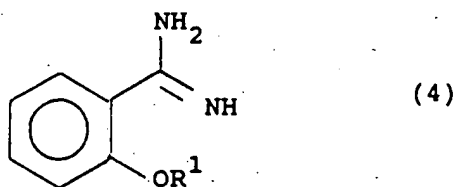
is a group of sub-formula (b).

10. A process according to claim 1 for preparing a compound which is :
- 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido [4,5-d]pyrimidine,
 - 7-phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido [4,5-d]pyrimidine,
 - 7-(3-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(3-methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine hydrochloride,
 - 7-(3-methylsulfinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(3-methylsulphonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 4,7-dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidine,
 - 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-ethoxycarbonylethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2,2,2-trifluoroethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(N-ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine, or
 - 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[5,4-d]pyrimidine,
 - or a pharmaceutically acceptable salt thereof.

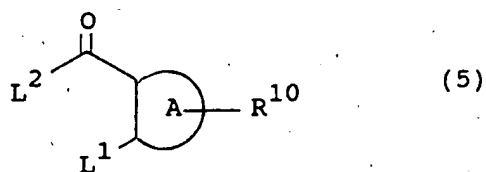
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11. A process according to claim 1 wherein L¹ is halo.

12. A process for preparing a pharmaceutical composition which comprises bringing into association a compound of the formula (1) as defined in any one of claims 1 to 10 and a pharmaceutically acceptable carrier.
13. A process for preparing a compound of the formula (2) as defined in claim 1 which comprises reacting a compound of the formula (4):



wherein R¹ is as defined in claim 1,
with a compound of the formula (5):

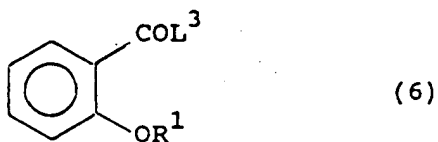


wherein L² is a leaving group and L¹, R¹⁰ and

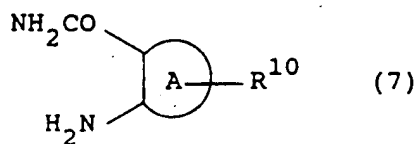


are as defined in claim 1.

14. A process for preparing a compound of the formula (3) as defined in claim 1 which comprises reacting a compound of the formula (6):



wherein R¹ is as defined in claim 1 and L³ is halo,
with a compound of the formula (7):



wherein R¹⁰ and



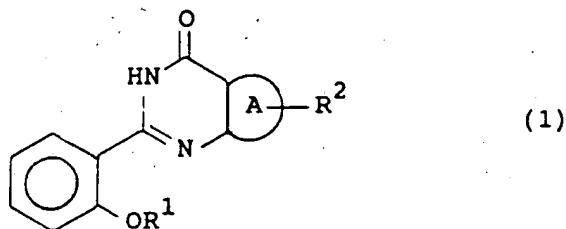
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are as defined in claim 1.

Claims for the following Contracting State: GR

10 1. A process for preparing a compound of the formula (1) :

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or a pharmaceutically acceptable salt thereof, wherein

R¹ is C₁-₆ alkyl, C₂-₆ alkenyl, C₃-₅ cycloalkyl, C₁-₆ alkyl, or C₁-₆ alkyl substituted by 1 to 6 fluoro groups;

25

R² is C₁-₆ alkylthio, C₁-₆ alkylsulphonyl, C₁-₆ alkoxy, hydroxy, hydrogen, hydrazino, C₁-₆ alkyl, phenyl, -NHCOR³ wherein R³ is hydrogen or C₁-₆ alkyl, or -NR⁴R⁵, wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R⁴ and R⁵ are independently hydrogen, C₃-₅ cycloalkyl or C₁-₆ alkyl which is optionally substituted by -CF₃, phenyl, -S(O)-_nC₁-₆ alkyl wherein n is 0, 1 or 2, -OR⁶, -CO₂R⁷ or -NR⁸R⁹ wherein R⁶ to R⁹ are independently hydrogen or C₁-₆ alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -S(O)_nC₁-₆ alkyl, -OR⁶ or -NR⁸R⁹ groups; and

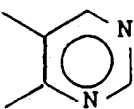
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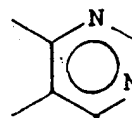


is a ring of sub-formula (a) or (b) :

40



(a)



(b) ,

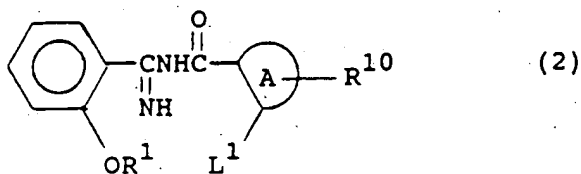
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which process comprises:

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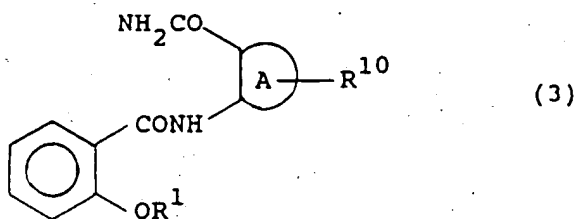
a) cyclising a compound of the formula (2) :



10 wherein L¹ is a displaceable group, R¹ and



are as hereinbefore defined and R¹⁰ is a group R² as hereinbefore defined or a precursor thereof; or
b) cyclising a compound of the formula (3) :



25 wherein R¹, R¹⁰ and



35 are as hereinbefore defined;
and thereafter where necessary :

- 40
- converting a group R¹⁰ to a group R²;
 - optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 for preparing a compound wherein R¹ is C₂-₅ alkyl.

45 3. A process according to claim 1 for preparing a compound wherein R¹ is n-propyl.

4. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is C₁-₆ alkylthio, C₁-₆ alkylsulphonyl or C₁-₆ alkoxy.

50 5. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is hydrogen, hydroxy or hydrazino.

6. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is phenyl or C₁-₆ alkyl.

55 7. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is -NHCOR³ or -NR⁴R⁵.

8. A process according to any one of claims 1 to 7 for preparing a compound wherein



is a group of sub-formula (a).

9. A process according to any one of claims 1 to 7 for preparing a compound wherein



is a group of sub-formula (b).

10. A process according to claim 1 for preparing a compound which is :
- 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(3-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(3-methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine hydrochloride,
 - 7-(3-methylsulphanylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(3-methylsulphonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 4,7-dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidine,
 - 7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-ethoxycarbonylethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2-carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-(2,2,2-trifluoroethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 - 7-propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,

7-(N-ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
 7-(2-phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine, or
 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[5,4-d]pyrimidine,
 or a pharmaceutically acceptable salt thereof.

11. A process according to claim 1 wherein L¹ is halo.

12. A process for preparing a pharmaceutical composition which comprises bringing into association a
 compound of the formula (1) as defined in any one of claims 1 to 10 and a pharmaceutically acceptable
 carrier.

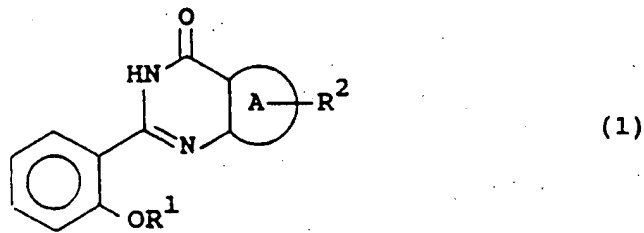
13. A compound of the formula (2) as defined in claim 1.

14. A compound of the formula (3) as defined in claim 1.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel (1)

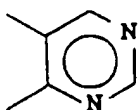


oder ein pharmazeutisch verträgliches Salz davon, wobei R¹ ein C₁₋₆-Alkyl-, C₂₋₆-Alkenyl-, C₃₋₅-Cycloalkyl-C₁₋₆-alkylrest oder ein mit 1 bis 6 Fluoratomen substituierter C₁₋₆-Alkylrest ist;

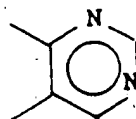
R² ein C₁₋₆-Alkylthio-, C₁₋₆-Alkylsulfonyl-, C₁₋₆-Alkoxyrest, eine Hydroxylgruppe, ein Wasserstoffatom, eine Hydrazingruppe, ein C₁₋₆-Alkylrest, eine Phenylgruppe, eine Gruppe -NHCOR³, wobei R³ ein Wasserstoffatom oder ein C₁₋₆-Alkylrest ist, oder eine Gruppe -NR⁴R⁵, wobei R⁴ und R⁵ zusammen mit dem Stickstoffatom, an das sie angebunden sind, einen Pyrrolidin-, Piperidin-, Hexahydroazepin-, Morpholin- oder Piperazinring bilden oder R⁴ und R⁵ unabhängig voneinander Wasserstoffatome, C₃₋₅-Cycloalkyl- oder C₁₋₆-Alkylreste, gegebenenfalls mit -CF₃, Phenyl, -S(O)_nC₁₋₆-Alkyl, wobei n die Zahl 0, 1 oder 2 ist, -OR⁶, -CO₂R⁷ oder -NR⁸R⁹, wobei R⁶ bis R⁹ unabhängig voneinander Wasserstoffatome oder C₁₋₆-Alkylreste sind, substituiert, mit der Maßgabe, daß das Kohlenstoffatom, das dem Stickstoffatom benachbart ist, nicht durch die -S(O)_nC₁₋₆-Alkyl-, -OR⁶ oder -NR⁸R⁹-Reste substituiert ist; und



ein Ring der Unterformel (a) oder (b) ist:



(a)



(b)

10

2. Verbindungen nach Anspruch 1, wobei R^1 ein C_{2-5} -Alkylrest ist.

3. Verbindung nach Anspruch 1, wobei R^1 eine n-Propylgruppe ist.

15

4. Verbindung nach einem der Ansprüche 1 bis 3, wobei R^2 ein C_{1-6} -Alkylthio-, C_{1-6} -Alkylsulfonyl- oder C_{1-6} -Alkoxyrest ist.

5. Verbindung nach einem der Ansprüche 1 bis 3, wobei R^2 ein Wasserstoffatom, eine Hydroxyl- oder Hydrazingruppe ist.

20

6. Verbindung nach einem der Ansprüche 1 bis 3, wobei R^2 eine Phenylgruppe oder ein C_{1-6} -Alkylrest ist.

7. Verbindung nach einem der Ansprüche 1 bis 3, wobei R^2 eine Gruppe $-NHCOR^3$ oder $-NR^4R^5$ ist.

25

8. Verbindung nach einem der Ansprüche 1 bis 7, wobei

30



eine Gruppe der Unterformel (a) ist.

35 9. Verbindung nach einem der Ansprüche 1 bis 7, wobei

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eine Gruppe der Unterformel (b) ist.

10. Verbindung nach Anspruch 1, nämlich

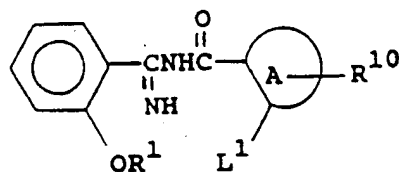
- 45 7-Methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin,
 50 7-Methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 55 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,

- 7-Methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin,
 5 7-Acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(3-Hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 10 7-(2-Hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(3-Methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin hydrochlorid,
 7-(3-Methylsulfinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(3-Methylsulfonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 15 4,7-Dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidin;
 7-Methylsulfonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin,
 7-(2-Ethoxycarbonylethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(Ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 20 7-(2-Carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(Carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2,2,2-Trifluorethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 25 7-Propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(N-Ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin, oder
 30 4-Oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[5,4-d]-pyrimidin,
 ist oder ein pharmazeutisch verträgliches Salz davon.

11. Verbindung nach einem der Ansprüche 1 bis 10 zur Verwendung als Medikament.
12. Arzneimittel, umfassend eine Verbindung nach einem der Ansprüche 1 bis 10 und einen pharmazeu-
 35 tisch verträglichen Träger.
13. Verfahren zur Herstellung einer Verbindung der Formel (1) oder eines pharmazeutisch verträglichen Salzes davon nach Anspruch 1, umfassend:
 a) Cyclisierung einer Verbindung der Formel (2):

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(2)

wobei L¹ eine verschiebbare Gruppe ist, R¹ und

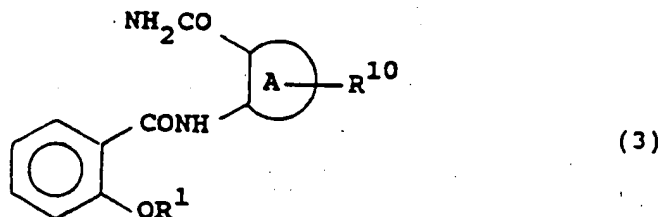
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wie in Anspruch 1 definiert sind und R¹⁰ eine wie in Anspruch 1 definierte Gruppe R² oder ein Vorläufer davon ist; oder

b) Cyclisieren einer Verbindung der Formel (3):



wobei R¹, R¹⁰ und



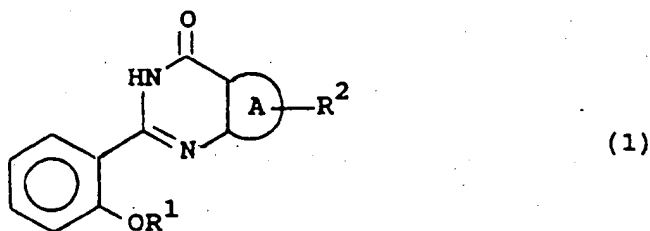
20 wie vorstehend definiert sind; und anschließend falls notwendig:
Umwandeln einer Gruppe R¹⁰ in eine Gruppe R²; gegebenenfalls die Bildung eines pharmazeutisch
verträglichen Salzes.

25 14. Verbindung nach Formel (2) wie in Anspruch 13 definiert.

15. Verbindung nach Formel (3) wie in Anspruch 13 definiert.

Patentansprüche für folgenden Vertragsstaat : ES

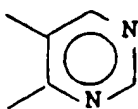
30 1. Verfahren zur Herstellung einer Verbindung der Formel (1)



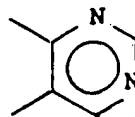
oder ein pharmazeutisch verträgliches Salz davon, wobei R¹ ein C₁-₆-Alkyl-, C₂-₆-Alkenyl-, C₃-₅-Cycloalkyl-C₁-₆-alkylrest oder ein mit 1 bis 6 Fluoratomen substituierter C₁-₆-Alkylrest ist;
R² ein C₁-₆-Alkylthio-, C₁-₆-Alkylsulfonyl-, C₁-₆-Alkoxyrest, eine Hydroxylgruppe, ein Wasserstoffatom,
45 eine Hydrazingruppe, ein C₁-₆-Alkylrest, eine Phenylgruppe, eine Gruppe -NHCOR³, wobei R³ ein
Wasserstoffatom oder ein C₁-₆-Alkylrest ist, oder eine Gruppe -NR⁴R⁵, wobei R⁴ und R⁵ zusammen
mit dem Stickstoffatom, an das sie angebunden sind, einen Pyrrolidin-, Piperidin-, Hexahydroazepin-,
Morpholin- oder Piperazinring bilden oder R⁴ und R⁵ unabhängig voneinander Wasserstoffatome, C₃-₅-
Cycloalkyl- oder C₁-₆-Alkylreste, gegebenenfalls mit -CF₃, Phenyl, -S(O)ₙC₁-₆-Alkyl, wobei n die Zahl
50 0, 1 oder 2 ist, -OR⁵, -CO₂R⁷ oder -NR⁸R⁹, wobei R⁵ bis R⁹ unabhängig voneinander Wasserstoffato-
me oder C₁-₆-Alkylreste sind, substituiert, mit der Maßgabe, daß das Kohlenstoffatom, das dem
Stickstoffatom benachbart ist, nicht durch die -S(O)ₙC₁-₆-Alkyl-, -OR⁵ oder -NR⁸R⁹-Reste substituiert
ist; und



ein Ring der Unterformel (a) oder (b) ist:

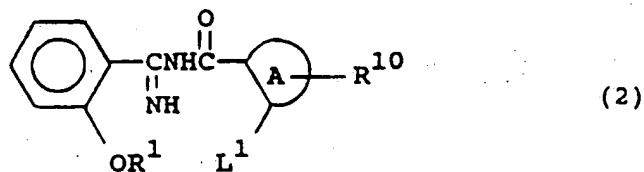


(a)



(b),

a) Cyclisierung einer Verbindung der Formel (2):

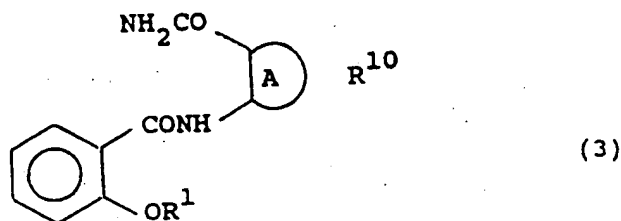


wobei L¹ eine verschiebbare Gruppe ist, R¹ und



wie in Anspruch 1 definiert sind und R¹⁰ eine wie in Anspruch 1 definierte Gruppe R² oder ein Vorläufer davon ist; oder

b) Cyclisieren einer Verbindung der Formel (3):



wobei R¹, R¹⁰ und



wie vorstehend definiert sind; und anschließend falls notwendig:
Umwandeln einer Gruppe R¹⁰ in eine Gruppe R²; gegebenenfalls die Bildung eines pharmazeutisch verträglichen Salzes.

2. Verfahren nach Anspruch 1, zur Herstellung einer Verbindung, in der R¹ ein C₂-5-Alkylrest ist.
3. Verfahren nach Anspruch 1, zur Herstellung einer Verbindung, in der R¹ eine n-Propylgruppe ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, zur Herstellung einer Verbindung, in der R² ein C₁₋₆-Alkylthio-, C₁₋₆-Alkylsulfonyl- oder C₁₋₆-Alkoxyrest ist.
5. Verfahren nach einem der Ansprüche 1 bis 3, zur Herstellung einer Verbindung, in der R² ein Wasserstoffatom, eine Hydroxyl- oder Hydrazingruppe ist.
6. Verfahren nach einem der Ansprüche 1 bis 3, zur Herstellung einer Verbindung, in der R² eine Phenylgruppe oder ein C₁₋₆-Alkylrest ist.
7. Verfahren nach einem der Ansprüche 1 bis 3, zur Herstellung einer Verbindung, in der R² eine Gruppe -NHCOR³ oder -NR⁴R⁵ ist.
8. Verfahren nach einem der Ansprüche 1 bis 7, zur Herstellung einer Verbindung, in der



eine Gruppe der Unterformel (a) ist.

9. Verfahren nach einem der Ansprüche 1 bis 7, zur Herstellung einer Verbindung, in der

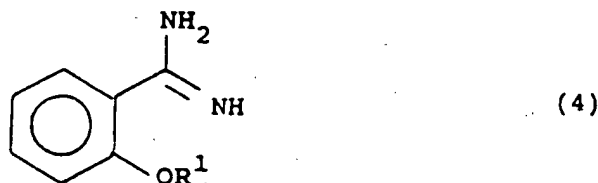


eine Gruppe der Unterformel (b) ist.

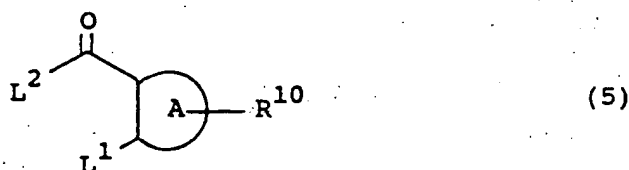
10. Verfahren nach Anspruch 1 zur Herstellung von
- 7-Methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin,
 7-Acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(3-Hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(3-Methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin hydrochlorid,
 7-(3-Methylsulfinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,

- 7-(3-Methylsulfonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 4,7-Dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidin;
 7-Methylsulfonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin,
 7-(2-Ethoxycarbonylethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin;
 7-(Ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(Carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2,2,2-Trifluorethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(N-Ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin, oder
 4-Oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[5,4-d]-pyrimidin,
 oder eines pharmazeutisch verträglichen Salzes davon.

11. Verfahren nach Anspruch 1, wobei L¹ ein Halogenatom ist.
 12. Verfahren zur Herstellung eines Arzneimittels, umfassend das Zusammenbringen einer Verbindung der Formel (1), wie in einem der Ansprüche 1 bis 10 definiert und einen pharmazeutisch verträglichen Träger.
 13. Verfahren zur Herstellung einer Verbindung der Formel (2) wie in Anspruch 1 definiert, umfassend das Umsetzen einer Verbindung der Formel (4)



wobei R¹ wie in Anspruch 1 definiert ist mit einer Verbindung der Formel (5):

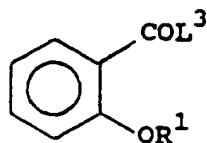


wobei L² eine Angangsgruppe und L¹, R¹⁰ und



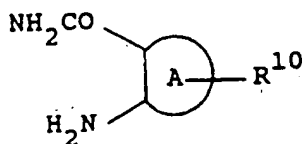
wie in Anspruch 1 definiert sind.

14. Verfahren zur Herstellung einer Verbindung der Formel (3) wie in Anspruch 1 definiert, umfassend das Umsetzen einer Verbindung der Formel (6):



(6)

wobei R^1 wie in Anspruch 1 definiert ist und L^3 ein Halogenatom ist, mit einer Verbindung der Formel (7):



(7)

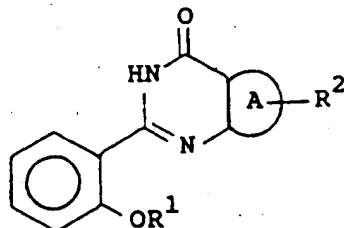
wobei R^{10} und



wie in Anspruch 1 definiert ist.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verfahren zur Herstellung einer Verbindung der Formel (1)

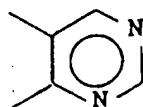


(1)

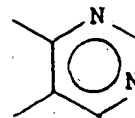
oder ein pharmazeutisch verträgliches Salz davon, wobei R^1 ein C_{1-6} -Alkyl-, C_{2-6} -Alkenyl-, C_{3-5} -Cycloalkyl- C_{1-6} -alkylrest oder ein mit 1 bis 6 Fluoratomen substituierter C_{1-6} -Alkylrest ist; R^2 ein C_{1-6} -Alkylthio-, C_{1-6} -Alkylsulfonyl-, C_{1-6} -Alkoxyrest, eine Hydroxylgruppe, ein Wasserstoffatom, eine Hydrazingruppe, ein C_{1-6} -Alkylrest, eine Phenylgruppe, eine Gruppe $-NHCOR^3$, wobei R^3 ein Wasserstoffatom oder ein C_{1-6} -Alkylrest ist, oder eine Gruppe $-NR^4R^5$, wobei R^4 und R^5 zusammen mit dem Stickstoffatom, an das sie angebunden sind, einen Pyrrolidin-, Piperidin-, Hexahydroazepin-, Morpholin- oder Piperazinring bilden oder R^4 und R^5 unabhängig voneinander Wasserstoffatome, C_{3-5} -Cycloalkyl- oder C_{1-6} -Alkylreste, gegebenenfalls mit $-CF_3$, Phenyl, $-S(O)_nC_{1-6}$ -Alkyl, wobei n die Zahl 0, 1 oder 2 ist, $-OR^6$, $-CO_2R^7$ oder $-NR^8R^9$, wobei R^6 bis R^9 unabhängig voneinander Wasserstoffatome oder C_{1-6} -Alkylreste sind, substituiert, mit der Maßgabe, daß das Kohlenstoffatom, das dem Stickstoffatom benachbart ist, nicht durch die $-S(O)_nC_{1-6}$ -Alkyl-, $-OR^6$ oder $-NR^8R^9$ -Reste substituiert ist; und



ein Ring der Unterformel (a) oder (b) ist:



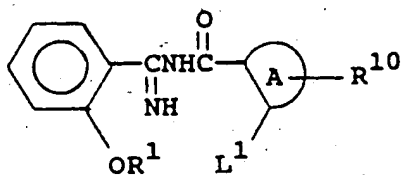
(a)



(b),

umfassend

a) Cyclisierung einer Verbindung der Formel (2):



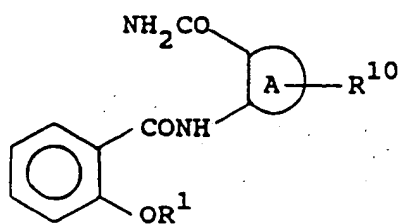
(2)

wobei L¹ eine verschiebbare Gruppe ist, R¹ und



wie in Anspruch 1 definiert sind und R¹⁰ eine wie in Anspruch 1 definierte Gruppe R² oder ein Vorläufer davon ist; oder

b) Cyclisieren einer Verbindung der Formel (3):



(3)

wobei R¹, R¹⁰ und



wie vorstehend definiert sind; und anschließend falls notwendig:

Umwandeln einer Gruppe R¹⁰ in eine Gruppe R²; gegebenenfalls die Bildung eines pharmazeutisch verträglichen Salzes.

2. Verfahren nach Anspruch 1, zur Herstellung einer Verbindung, in der R¹ ein C₂-5-Alkylrest ist.
3. Verfahren nach Anspruch 1, zur Herstellung einer Verbindung, in der R¹ eine n-Propylgruppe ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, zur Herstellung einer Verbindung, in der R² ein C₁-₆-Alkylthio-, C₁-₆-Alkylsulfonyl- oder C₁-₆-Alkoxyrest ist.
5. Verfahren nach einem der Ansprüche 1 bis 3, zur Herstellung einer Verbindung, in der R² ein Wasserstoffatom, eine Hydroxyl- oder Hydrazingruppe ist.
6. Verfahren nach einem der Ansprüche 1 bis 3, zur Herstellung einer Verbindung, in der R² eine Phenylgruppe oder ein C₁-₆-Alkylrest ist.
7. Verfahren nach einem der Ansprüche 1 bis 3, zur Herstellung einer Verbindung, in der R² eine Gruppe -NHCOR³ oder -NR⁴R⁵ ist.
8. Verfahren nach einem der Ansprüche 1 bis 7, zur Herstellung einer Verbindung, in der



eine Gruppe der Unterformel (a) ist.

9. Verfahren nach einem der Ansprüche 1 bis 7, zur Herstellung einer Verbindung, in der



eine Gruppe der Unterformel (b) ist.

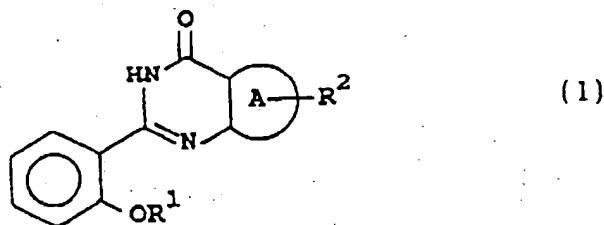
10. Verfahren nach Anspruch 1 zur Herstellung von
- 7-Methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido-[4,5-d]pyrimidin,
 7-Cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin,
 7-Acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(3-Hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(3-Methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin hydrochlorid,
 7-(3-Methylsulfinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,

- 7-(3-Methylsulfonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 4,7-Dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidin;
 7-Methylsulfonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin,
 7-(2-Ethoxycarbonyl-ethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(Ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(Carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2,2,2-Trifluorethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(N-Ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-Dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin,
 7-(2-Phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin, oder
 4-Oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[5,4-d]-pyrimidin,
 ist oder eines pharmazeutisch verträglichen Salzes davon.
11. Verfahren nach Anspruch 1, wobei L¹ ein Halogenatom ist.
12. Verfahren zur Herstellung eines Arzneimittels, umfassend das Zusammenbringen einer Verbindung der Formel (1), wie in einem der Ansprüche 1 bis 10 definiert und eines pharmazeutisch verträglichen Trägers.
13. Verbindung nach Formel (2) wie in Anspruch 1 definiert.
14. Verbindung nach Formel (3) wie in Anspruch 1 definiert.

Revendications

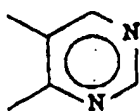
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule (1) :

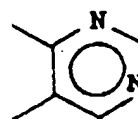


ou sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle :

- R¹ est un groupe alkyle en C₁₋₆, alcényle en C₂₋₆, cycloalkyl(en C₃₋₅)-alkyle en C₁₋₆ ou alkyle en C₁₋₆ substitué par 1 à 6 atomes de fluor;
- R² est un groupe alkylthio en C₁₋₆, alkylsulfonyl en C₁₋₆, alcoxy en C₁₋₆, hydroxy, un atome d'hydrogène, un groupe hydrazino, alkyle en C₁₋₆, phényle, -NHCOR³ dans lequel R³ est un atome d'hydrogène ou un groupe alkyle en C₁₋₆, ou -NR⁴R⁵, dans lequel R⁴ et R⁵ forment ensemble avec l'atome d'azote auquel ils sont fixés, un cycle pyrrolidino, pipéridino, hexahydroazépino, morpholino ou pipérazino ou bien R⁴ et R⁵ sont indépendamment un atome d'hydrogène un groupe cycloalkyle en C₃₋₅ ou alkyle en C₁₋₆ qui est éventuellement substitué par un groupe -CF₃, phényle, -S(O)_n-alkyle en C₁₋₆ dans lequel n est 0, 1 ou 2, -OR⁶, -CO₂R⁷ ou -NR⁸R⁹ dans lesquels R₆ à R₉ sont indépendamment un atome d'hydrogène ou un groupe alkyle en C₁₋₆, à condition que l'atome de carbone adjacent à l'atome d'azote ne soit pas substitué par ces groupes -S(O)_n-alkyle en C₁₋₆, -OR⁶ ou -NR⁸R⁹; et est un cycle représenté par la sous-formule (a) ou (b) :



(a)



(b)

5

10

2. Composé suivant la revendication 1, dans lequel R¹ est un groupe alkyle en C₂₋₅.
3. Composé suivant la revendication 1, dans lequel R¹ est un groupe n-propyle.
- 15 4. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R² est un groupe alkylthio en C₁₋₆, alkylsulfonyl en C₁₋₆ ou alcoxy en C₁₋₆.
5. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R² est un atome d'hydrogène, un groupe hydroxy ou hydrazino.
- 20 6. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R² est un groupe phényle ou alkyle en C₁₋₆.
7. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R² est un groupe -NHCOR³ ou bien -NR⁴R⁵.
- 25 8. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel

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est un groupe de sous-formule (a).

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9. Composé suivant l'une quelconque des revendications 1 à 7, dans lequel

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est un groupe de sous-formule (b).

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10. Composé suivant la revendication 1, qui est :
 - la 7-méthylthio-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 7-méthylthio-4-oxo-2-(2-éthoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 7-méthylthio-4-oxo-2-(2-méthoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 7-méthylthio-4-oxo-2-(2-isobutoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - 50 la 7-méthylthio-4-oxo-2-(2-cyclopropylméthoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 7-méthylthio-4-oxo-2-(2-allyloxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 7-amino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 7-méthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 7-diméthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - 55 la 7-hydrazino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 7-éthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;
 - la 7-(2-hydroxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido[4,5-d]-pyrimidine;

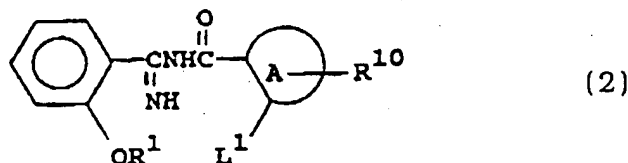
- la 7-éthyl-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-méthylamino-4-oxo-2-(2-méthoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-phényl-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-morpholino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 5 la 7-cyclopropylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-acétamido-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-propylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(3-hydroxypropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-méthoxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 10 la 7-(2-diméthylaminoéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-hydroxypropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(3-méthylthiopropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-aminoéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(3-méthylsulfinylpropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 15 ne;
 la 7-(3-méthylsulfonylpropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 ne;
 la 4,7-dioxo-2-(2-propoxyphényl)-3,4,7,8-tétrahydropyrimido-[4,5-d]-pyrimidine;
 la 7-méthylsulfonyl-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 20 la 7-diéthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-éthoxycarbonyléthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 ne;
 la 7-(éthoxycarbonylméthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-carboxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 25 la 7-(carboxyméthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-éthoxy-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-méthoxy-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2,2,2-trifluoroéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-propoxy-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 30 la 7-(N-éthyl-N-hydroxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 ne;
 la 7-dipropylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-phénéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine ou
 la 4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[5,4-d]-pyrimidine,
 35 ou un sel de celles-ci acceptable du point de vue pharmaceutique.

11. Composé suivant l'une quelconque des revendications 1 à 10, utilisable comme médicament.

12. Composition pharmaceutique, qui comprend un composé suivant l'une quelconque des revendications 1 à 10 et un support acceptable du point de vue pharmaceutique.

13. Procédé pour préparer un composé de formule (1) ou un sel de celui-ci acceptable du point de vue pharmaceutique tel que défini dans la revendication 1, qui comprend :

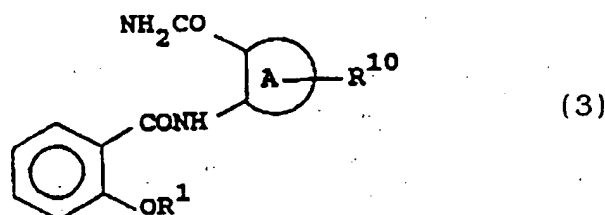
(a) la cyclisation d'un composé de formule (2) :



dans laquelle L¹ est un groupe pouvant être déplacé, R¹ et



sont tels que définis dans la revendication 1, et R^{10} est un groupe R^2 tel que défini dans la revendication 1 ou un précurseur de celui-ci; ou
(b) la cyclisation d'un composé de formule (3) :



dans laquelle R^1 , R^{10} et



sont tels que définis plus haut;
et ensuite, si cela est nécessaire :

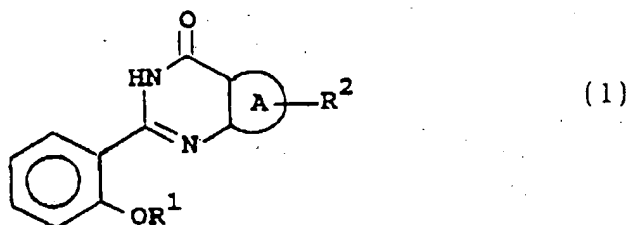
- la conversion d'un groupe R^{10} en un groupe R^2 ;
- la formation éventuelle d'un sel acceptable du point de vue pharmaceutique.

14. Composé de formule (2) telle que définie la revendication 13.

15. Composé de formule (3) telle que définie la revendication 13.

Revendications pour l'Etat contractant suivant : ES

1. Procédé pour préparer un composé de formule (1):



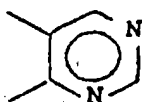
ou un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle :

- R^1 est un groupe alkyle en C_{1-6} , alcényle en C_{2-6} , cycloalkyl(en C_{3-5})-alkyle en C_{1-6} ou alkyle en C_{1-6} substitué par 1 à 6 atomes de fluor;
- R^2 est un groupe alkylthio en C_{1-6} , alkylsulfonyl en C_{1-6} , alcoxy en C_{1-6} , hydroxy, un atome d'hydrogène, un groupe hydrazino, alkyle en C_{1-6} , phényle, $-NHCOR^3$ dans lequel R^3 est un atome d'hydrogène ou un groupe alkyle en C_{1-6} , ou $-NR^4R^5$, dans lequel R^4 et R^5 forment ensemble avec l'atome d'azote auquel ils sont fixés, un cycle pyrrolidino, pipéridino, hexahydroazépino, morpholino ou pipérazino, ou bien R^4 et R^5 sont indépendamment un atome d'hydrogène, un groupe cycloalkyle en C_{3-5} ou alkyle en C_{1-6} qui est éventuellement

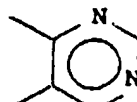
substitué par un groupe $-CF_3$, phényle, $-S(O)_n$ -alkyle en C_{1-6} dans lequel n est 0, 1 ou 2, $-OR^6$, $-CO_2R^7$ ou $-NR^8R^9$ dans lesquels R_6 à R_9 sont indépendamment un atome d'hydrogène ou un groupe alkyle en C_{1-6} , à condition que l'atome de carbone adjacent à l'atome d'azote ne soit pas substitué par ces groupes $-S(O)_n$ -alkyle en C_{1-6} , $-OR^6$ ou $-NR^8R^9$; et



est un cycle représenté par la sous-formule (a) ou (b) :



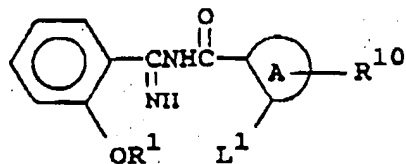
(a)



(b)

lequel procédé comprend :

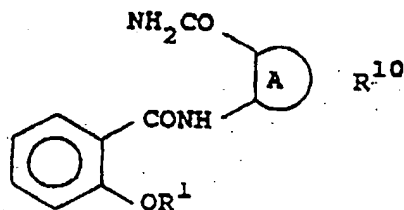
(a) la cyclisation d'un composé de formule (2) :



(2)

dans laquelle L^1 est un groupe pouvant être déplacé, R^1 et sont tels que définis plus haut, et R^{10} est un groupe R^2 tel que défini plus haut ou un précurseur de celui-ci; ou

(b) la cyclisation d'un composé de formule (3) :



(3)

dans laquelle R^1 , R^{10} et



sont tels que définis plus haut;
et ensuite, si cela est nécessaire :

- la conversion d'un groupe R^{10} en un groupe R^2 ;
- la formation éventuelle d'un sel acceptable du point de vue pharmaceutique.

2. Procédé suivant la revendication 1, pour préparer un composé dans lequel R¹ est un groupe alkyle en C₂₋₅.
3. Procédé suivant la revendication 1, pour préparer un composé dans lequel R¹ est un groupe n-propyle.
4. Procédé suivant l'une quelconque des revendications 1 à 3, pour préparer un composé dans lequel R² est un groupe alkylthio en C₁₋₆, alkylsulfonyl en C₁₋₆ ou alcoxy en C₁₋₆.
5. Procédé suivant l'une quelconque des revendications 1 à 3, pour préparer un composé dans lequel R² est un atome d'hydrogène, un groupe hydroxy ou hydrazino.
6. Procédé suivant l'une quelconque des revendications 1 à 3, pour préparer un composé dans lequel R² est un groupe phényle ou alkyle en C₁₋₆.
7. Procédé suivant l'une quelconque des revendications 1 à 3, pour préparer un composé dans lequel R² est un groupe -NHCOR³ ou bien -NR⁴R⁵.
8. Procédé suivant l'une quelconque des revendications 1 à 7, pour préparer un composé dans lequel



est un groupe de sous-formule (a).

9. Procédé suivant l'une quelconque des revendications 1 à 7, pour préparer un composé dans lequel



est un groupe de sous-formule (b).

10. Procédé suivant la revendication 1, pour préparer un composé qui est :
 - la 7-méthylthio-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-méthylthio-4-oxo-2-(2-éthoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-méthylthio-4-oxo-2-(2-méthoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-méthylthio-4-oxo-2-(2-isobutoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-méthylthio-4-oxo-2-(2-cyclopropylméthoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-méthylthio-4-oxo-2-[2-allyloxyphényl]-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-amino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-méthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-diméthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-hydrazino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-éthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-(2-hydroxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-éthyl-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-méthylamino-4-oxo-2-(2-méthoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-phényl-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-morpholino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-cyclopropylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-acétamido-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-propylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-(3-hydroxypropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-(2-méthoxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 - la 7-(2-diméthylaminoéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

ne;

la 7-(2-hydroxypropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-(3-méthylthiopropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-(2-aminoéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-(3-méthylsulfinylpropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

ne;

la 7-(3-méthylsulfonylpropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

ne;

la 4,7-dioxo-2-(2-propoxyphényl)-3,4,7,8-tétrahydropyrimido-[4,5-d]-pyrimidine;

la 7-méthylsulfonyl-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-diéthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-(2-éthoxycarbonyléthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

ne;

la 7-(éthoxycarbonylméthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

ne;

la 7-(2-carboxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-(carboxyméthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-éthoxy-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-méthoxy-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-(2,2,2-trifluoroéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-propoxy-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-(N-éthyl-N-hydroxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

ne;

la 7-dipropylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

la 7-(2-phénéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine ou

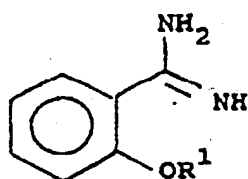
la 4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[5,4-d]-pyrimidine,

ou un sel de celles-ci acceptable du point de vue pharmaceutique.

11. Procédé suivant la revendication 1, dans lequel L' est un atome d'halogène.

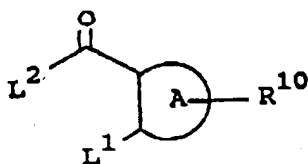
12. Procédé pour préparer une composition pharmaceutique, qui comprend la mise en association d'un composé de formule (1) suivant l'une quelconque des revendications 1 à 10 et d'un support acceptable du point de vue pharmaceutique.

13. Procédé pour préparer un composé de formule (2) telle que définie dans la revendication 1, qui comprend la réaction d'un composé de formule (4) :



(4)

dans laquelle R' est tel que défini dans la revendication 1, avec un composé de formule (5) :



(5)

dans laquelle L² est un groupe mobile et L¹, R¹⁰ et

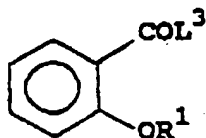


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sont tels que définis dans la revendication 1.

14. Procédé pour préparer un composé de formule (3) telle que définie dans la revendication 1, qui comprend la réaction d'un composé de formule (6) :

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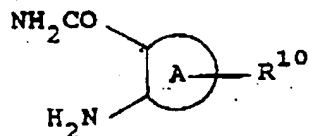


(6)

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dans laquelle R¹ est tel que défini dans la revendication 1 et L³ est un atome d'halogène, avec un composé de formule (7) :

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(7)

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dans laquelle R¹⁰ et

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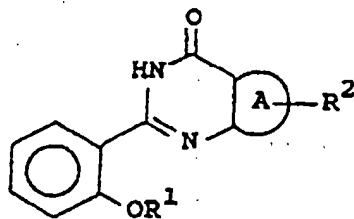
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sont tels que définis dans la revendication 1.

Revendications pour l'Etat contractant suivant : GR

1. Procédé pour préparer un composé de formule (1):

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(1)

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ou un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle :

R¹ est un groupe alkyle en C₁-₆, alcényle en C₂-₆, cycloalkyl(en C₃-₅)-alkyle en C₁-₆ ou alkyle en C₁-₆ substitué par 1 à 6 atomes de fluor;

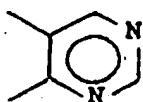
R² est un groupe alkylthio en C₁-₆, alkylsulfonyl en C₁-₆, alcoxy en C₁-₆, hydroxy, un atome d'hydrogène, un groupe hydrazino, alkyle en C₁-₆, phényle, -NHCOR³ dans lequel R³ est un atome d'hydrogène ou un groupe alkyle en C₁-₆, ou -NR⁴R⁵, dans lequel R⁴ et R⁵ forment ensemble avec l'atome d'azote auquel ils sont fixés, un cycle pyrrolidino, pipéridino, hexahydroazépino, morpholino ou pipérazino, ou bien R⁴ et R⁵ sont indépendamment un atome

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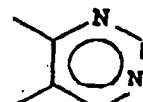
d'hydrogène, un groupe cycloalkyle en C₃₋₅ ou alkyle en C₁₋₆ qui est éventuellement substitué par un groupe -CF₃, phényle, -S(O)_n-alkyle en C₁₋₆ dans lequel n est 0, 1 ou 2, -OR⁶, -CO₂R⁷ ou -NR⁸R⁹ dans lesquels R₆ à R₉ sont indépendamment un atome d'hydrogène ou un groupe alkyle en C₁₋₆, à condition que l'atome de carbone adjacent à l'atome d'azote ne soit pas substitué par ces groupes -S(O)_n-alkyle en C₁₋₆, -OR⁶ ou -NR⁸R⁹; et



est un cycle représenté par la sous-formule (a) ou (b) :



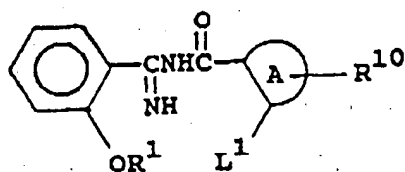
(a)



(b) ,

lequel procédé comprend :

(a) la cyclisation d'un composé de formule (2) :



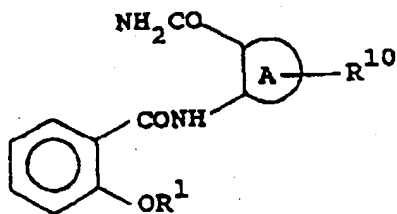
(2)

dans laquelle L¹ est un groupe pouvant être déplacé, R¹ et



sont tels que définis plus haut, et R¹⁰ est un groupe R² tel que défini plus haut ou un précurseur de celui-ci; ou

(b) la cyclisation d'un composé de formule (3) :



(3)

dans laquelle R¹, R¹⁰ et



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sont tels que définis plus haut;
et ensuite, si cela est nécessaire :

- la conversion d'un groupe R^{10} en un groupe R^2 ;
- la formation éventuelle d'un sel acceptable du point de vue pharmaceutique.

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2. Procédé suivant la revendication 1, pour préparer un composé dans lequel R^1 est un groupe alkyle en C_{2-5} .

3. Procédé suivant la revendication 1, pour préparer un composé dans lequel R^1 est un groupe n-propyle.

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4. Procédé suivant l'une quelconque des revendications 1 à 3, pour préparer un composé dans lequel R^2 est un groupe alkylthio en C_{1-6} , alkylsulfonyl en C_{1-6} ou alcoxy en C_{1-6} .

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5. Procédé suivant l'une quelconque des revendications 1 à 3, pour préparer un composé dans lequel R^2 est un atome d'hydrogène, un groupe hydroxy ou hydrazino.

6. Procédé suivant l'une quelconque des revendications 1 à 3, pour préparer un composé dans lequel R^2 est un groupe phényle ou alkyle en C_{1-6} .

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7. Procédé suivant l'une quelconque des revendications 1 à 3, pour préparer un composé dans lequel R^2 est un groupe $-NHCOR^3$ ou bien $-NR^4R^5$.

8. Procédé suivant l'une quelconque des revendications 1 à 7, pour préparer un composé dans lequel

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est un groupe de sous-formule (a).

9. Procédé suivant l'une quelconque des revendications 1 à 7, pour préparer un composé dans lequel

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est un groupe de sous-formule (b).

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10. Procédé suivant la revendication 1, pour préparer un composé qui est :

- la 7-méthylthio-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-méthylthio-4-oxo-2-(2-éthoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-méthylthio-4-oxo-2-(2-méthoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-méthylthio-4-oxo-2-(2-isobutoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-méthylthio-4-oxo-2-(2-cyclopropylméthoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-méthylthio-4-oxo-2-(2-allyloxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-amino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-méthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-diméthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-hydrazino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
- la 7-éthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;

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- la 7-(2-hydroxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-éthyl-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-méthylamino-4-oxo-2-(2-méthoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-phényl-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-morpholino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-cyclopropylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-acétamido-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-propylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(3-hydroxypropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-méthoxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-diméthylaminoéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 ne;
 la 7-(2-hydroxypropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(3-méthylthiopropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-aminoéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(3-méthylsulfinylpropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 ne;
 la 7-(3-méthylsulfonylpropylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 ne;
 la 4,7-dioxo-2-(2-propoxyphényl)-3,4,7,8-tétrahydropyrimido-[4,5-d]-pyrimidine;
 la 7-méthylsulfonyl-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-diéthylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-éthoxycarbonyléthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 ne;
 la 7-(éthoxycarbonylméthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 ne;
 la 7-(2-carboxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(carboxyméthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-éthoxy-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-méthoxy-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2,2,2-trifluoroéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-propoxy-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(N-éthyl-N-hydroxyéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 ne;
 la 7-dipropylamino-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine;
 la 7-(2-phénéthylamino)-4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[4,5-d]-pyrimidine ou
 la 4-oxo-2-(2-propoxyphényl)-3,4-dihydropyrimido-[5,4-d]-pyrimidine,
 ou un sel de celles-ci acceptable du point de vue pharmaceutique.

11. Procédé suivant la revendication 1, dans lequel L¹ est un atome d'halogène.
12. Procédé pour préparer une composition pharmaceutique, qui comprend la mise en association d'un composé de formule (1) suivant l'une quelconque des revendications 1 à 10 et d'un support acceptable du point de vue pharmaceutique.
13. Composé de formule (2) telle que définie la revendication 1.
14. Composé de formule (3) telle que définie la revendication 1.